Idiopathic anaphylaxis: Diagnosis and management

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ABSTRACT

Introduction: *Idiopathic anaphylaxis (IA) is a diagnosis of exclusion and is based on the inability to identify a causal relationship between a trigger and an anaphylactic event, despite a detailed patient history and careful diagnostic assessment. The prevalence of IA among the subset of people who experienced anaphylaxis is challenging to estimate and varies widely, from 10 to 60%; most commonly noted is ~20% in the adult anaphylactic population. Comorbid atopic conditions, such as food allergy, allergic rhinitis, and asthma, are present in up to 48% of patients with IA. Improved diagnostic technologies and an increased understanding of conditions that manifest with symptoms associated with anaphylaxis have improved the ability to determine a more accurate diagnosis for patients who may have been initially diagnosed with IA.*

Methods: *Literature search was conducted on PubMed, Google Scholar and Embase.*

Results: *Galactose-α-1,3-galactose (α-gal) allergy, mast cell disorders, and hereditary a-tryptasemia are a few differential diagnoses that should be considered in patients with IA. Unlike food allergy, when anaphylaxis occurs within minutes to 2 hours after allergen consumption, α-gal allergy is a 3–6-hour delayed immunoglobulin E–mediated anaphylactic reaction to a carbohydrate epitope found in red meat (e.g., beef, lamb, pork). The more recently described hereditary α-tryptasemia is an inherited autosomal dominant genetic trait caused by increased germline copies of tryptase human gene alpha-beta 1 (TPSAB1), which encodes α tryptase and is associated with elevated baseline serum tryptase. Acute management of IA consists of carrying an epinephrine autoinjector to be administered immediately at the first signs of anaphylaxis. Long-term management for IA with antihistamines and other agents aims to potentially reduce the frequency and severity of the anaphylactic reactions, although the evidence is limited. Biologics are potentially steroid-sparing for patients with IA; however, more research on IA therapies is needed.*

Conclusion: *The lack of diagnostic criteria, finite treatment options, and intricacies of making a differential diagnosis make IA challenging for patients and clinicians to manage.*

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ANAPHYLAXIS

Anaphylaxis is a severe allergic reaction that is rapid in onset and may cause death.[1] The more rapidly anaphylaxis develops, the more likely the reaction is to be severe and potentially life-threatening.[2] Consequently, the prompt recognition and treatment of the condition with epinephrine is imperative.[3] Anaphylaxis is a relatively rare condition, with a prevalence of 0.3% to as high as 2%, and seems to be increasing, particularly in the pediatric population.[2,4] A systematic review estimates that the incidence of anaphylaxis is 1.5–7.9 per 100,000 person-years, which indicates that 0.3% of the population will experience anaphylaxis in their lifetime.

Fortunately, the case fatality rates for anaphylaxis in population studies are low, <0.001%.[5] Medications (most often, antibiotics), food (peanuts, tree nuts, egg, seafood, fish, cow's milk, and wheat), and insect stings (bees and wasps) are the most commonly reported causes of nonfatal anaphylactic events, which represent 35, 32, and 19% of all cases, respectively.[4,6] Less frequent triggers of anaphylaxis include exercise, semen, food additives, hormonal changes (*i.e.*, menstrual factors), anesthesia, radiocontrast media, topical medications, transfusions, immune aggregates, and vaccines, including the COVID-19 (coronavirus disease 2019) vaccine.[3,7]

Diagnosis and Pathophysiology of Anaphylaxis

Targeted skin-prick testing (sometimes with fresh food antigens, when appropriate), specific immunoglobulin-E (sIgE), component-resolved diagnostics, and oral allergen challenges are key diagnostic tests for determining allergy within the context of a supportive clinical history.[8] Anaphylaxis can occur through immunologic mechanisms, both immunoglobulin E (IgE) mediated

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(*e.g.*, food, insect stings, medications) and non–IgE-mediated (*e.g.*, immune aggregates, complement system activation, coagulation system activation, autoimmune mechanisms, dextrans, nonsteroidal anti-inflammatory drugs), and through nonimmunologic mechanisms (*e.g.*, exercise, cold, medications [opioids]).[9,10] IgE-mediated mechanisms are the most well understood. When an individual who is sensitized re-encounters an antigen to which he or she is sensitized, sIgE antibodies bind and cross-link on the Fc epsilon receptor (FcεR) on mast cells (MC) and basophils, which lead to the degranulation and release of mediators, including histamine, platelet activating factor, leukotrienes, and prostaglandins. The release of these mediators results in smooth-muscle spasm, increases vascular permeability, which leads to vasodilation, myocardial depression, and activation of vagal effector pathways. MCs are found in large quantities beneath mucosal and cutaneous surfaces, which explains swelling in the oral cavity, gastrointestinal symptoms, and urticaria.[11]

Idiopathic Anaphylaxis

Idiopathic anaphylaxis (IA) is a diagnosis of exclusion and is based on the inability to identify a causal relationship between a trigger and an anaphylactic event, despite a detailed patient history and careful diagnostic assessment.[8,12] IA can be classified by frequency and by manifestation of the attack. Patients who experience six or more anaphylactic episodes per year or two or more episodes per month are classified as IA-frequent, whereas, those who experience fewer anaphylactic episodes are considered IA-infrequent.[13] The classification of IA determines the appropriate treatment recommendations, although no standard treatment guidelines exist (see Management of Idiopathic Anaphylaxis).[8]

The prevalence of IA among the subset of people who have anaphylaxis is challenging to estimate and highly dependent on the context in which the condition is diagnosed (*e.g.*, emergency department [ED] versus an allergy/immunology clinic).[14] The incidence and prevalence of IA vary widely, from 10 to 60%; most commonly reported is ~20% in the adult population.[15–19] For example, Wright *et al.*,[18] reported a 17% incidence of IA among 40 ED pediatric patients, and similarly, Gonzalez-Estrada *et al.*,[19] reported a 13.6% incidence rate in 730 ED pediatric and adult patients who presented with anaphylaxis. IA has been reported in people ages 5 years through 83 years old, more commonly in adults (84–96% of cases) and females (60%).[15,20] Comorbid atopic conditions such as food allergy, allergic rhinitis, and asthma are present in up to 48% of patients with IA.[15] Intermittent urticaria or angioedema also seems to increase the risk of IA.[16,21] IA can be life-threatening, and, although rare, fatalities have been reported.[22,23] Improved diagnostic technologies and an increased understanding of conditions that manifest with symptoms associated with anaphylaxis have improved the ability to determine a more accurate etiology of anaphylaxis in patients with IA.[24] However, the lack of diagnostic criteria and limited treatment options make IA burdensome for patients and clinicians to manage (Fig. 1).[25]

DIFFERENTIAL DIAGNOSIS

Alpha-Gal Allergy

Galactose-α-1,3-galactose (α-gal) allergy, also known as α-gal syndrome (AGS), was first identified in 2008 and 2009 as sensitization to the carbohydrate epitope, not protein epitopes, found in nonprimate mammalian meat or red meat (*e.g.*, beef, lamb, pork), and is also induced by cetuximab.[26,27] AGS affects adult, adolescent, and pediatric populations. Many patients in AGS cases were initially labeled as IA due to the delayed onset of anaphylaxis, which generally occurs 3 to 6 hours after exposure, which makes it challenging to identify the anaphylactic trigger.[28] Pattanaik *et al.*[28] found that IA decreased at a single center from 59% in 1978–2003 to 35% in 2006–2016 in adults and adolescents, and attributed the etiology of their IA to α-gal allergy. The prevalence of α-gal sIgE sensitization (>0.1 kUA/L indicates sensitization) ranges between 5.5 and 8.1% in the general adult population in urban environments, and is prevalent in tick endemic areas, which suggests the role of ticks in AGS development.[29,30] One study found that 18% of patients with clonal MC disorders were also sensitized to α-gal.[31]

Mast Cell Disorders

There exists an intriguing relationship between IA and MC activation syndrome (MCAS), often initially diagnosed as IA.[14] Across three studies, 14 to 47% of patients diagnosed with IA had underlying MC disorders on further evaluation.[12,32,33] Within the past decade, MCAS has evolved as an all-encompassing term proposed for MC-related disorders that are associated with higher rates of anaphylactic events.[34–36] Three criteria are needed to fulfill an MCAS diagnosis: symptomology attributable to MC activation; laboratory evidence of MC mediators such as elevated serum tryptase in the blood sera or N methylhistamine, prostaglandin D2 (PgD2) metabolites, or leukotriene E4 (LTE4) in urine; and control of symptoms with MC-directed therapies.[35] MCAS can be further classified into primary, secondary, and idiopathic categories.

Primary MCAS are characterized by the proliferation and accumulation of aberrant MCs, with the gain-of-function mutation in *KIT* (most commonly D816V) and

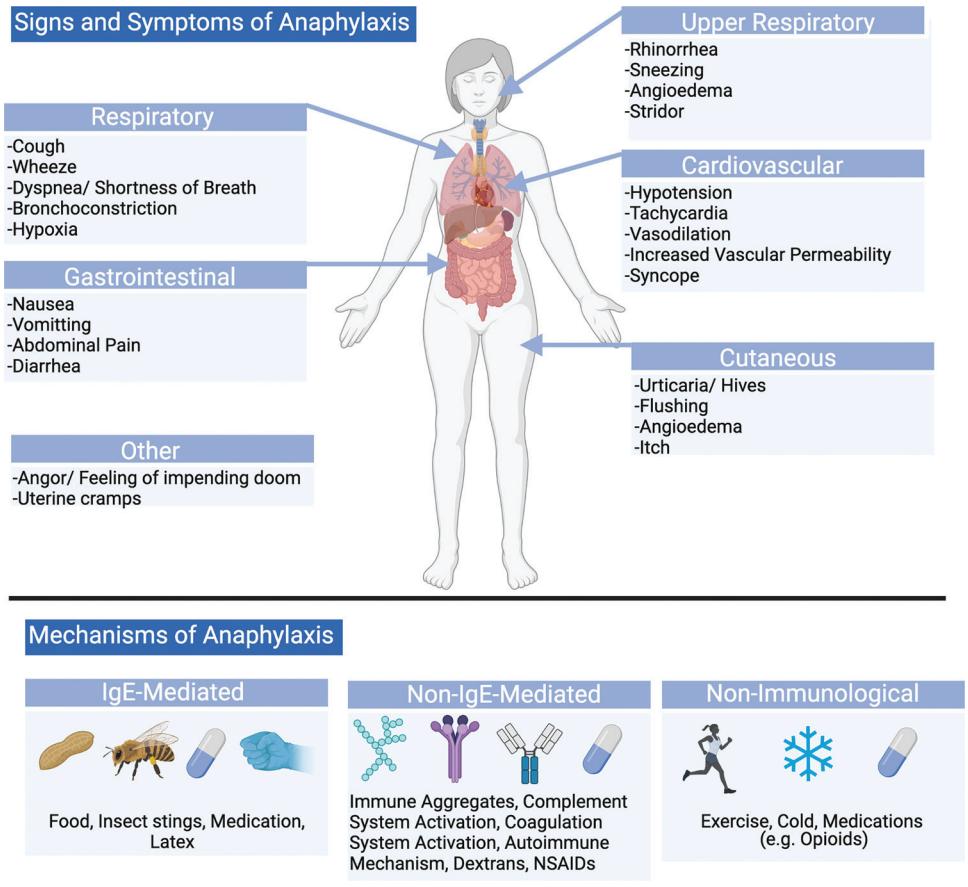

Figure 1. *Symptomology and mechanisms of anaphylaxis. The mediators released during an anaphylactic reaction can result in symptoms that affect the upper and lower respiratory tract, gastrointestinal tract, cardiovascular system, and skin. Mechanisms of anaphylaxis include: IgE mediated, non-IgE mediated, and nonimmunological causes. IgE = Immunoglobulin E.*

$CD2^+$ or $CD25^+$ MCs in the bone marrow or another organ. Primary MCAS includes systemic mastocytosis (baseline serum tryptase [bST] level > 20 ng/mL) and monoclonal MCAS (bST level < 20 ng/mL).[33] Secondary MCAS are nonclonal, and allergic triggers can be IgE and non-IgE mediated.[34,36] Idiopathic MCAS is classified by recurrent episodes of anaphylaxis, a lack of *KIT*, $CD2^+$, $CD25^+$ MC markers, normal bST levels, and elevated tryptase levels obtained within 4 hours of an anaphylactic episode (20% of baseline plus 2 ng/mL has been proposed and validated as a reliable marker of MC activation).[34,37] A *c-KIT* mutation and bone marrow biopsy are warranted to determine which MCAS a patient has. The Spanish Network on Mastocytosis (Red Española de Mastocitosis),[38] Karolinska score,[33] National Institutes of Health Idiopathic Clonal Anaphylaxis Score,[12] and World Health Organization[39] developed criteria and cutoff values to guide diagnosis.

Hereditary Alpha-Tryptasemia Syndrome

Hereditary alpha-tryptasemia (HAT) syndrome is an inherited autosomal dominant genetic trait caused by increased germline copies of *TPSAB1*, which encodes α tryptase.[40] Individuals with this trait have elevated bST levels and may present with symptoms that affect several organ systems, including systemic immediate hypersensitivity reactions, cutaneous flushing and pruritus, functional gastrointestinal diseases, connective tissue abnormalities, joint hypermobility, musculoskeletal pain, and neuropsychiatric symptoms, which may be similar to Ehlers-Danlos syndrome–like and postural orthostatic tachycardia–like symptoms.[40,41] An elevated bST level (>11.4 ng/mL) has been reported in 4–6% of the general population, which may be due to hereditary factors or other conditions, including clonal expansion of myeloid or MCs, including mastocytosis.[40,42,43] To date, HAT syndrome is believed to be inherited with full penetrance because all individuals identified have had bST levels of >8 ng/mL and each additional *TPSAB1* copy number results in a fold increase of bST levels (average bST level caused by duplication is 15 ± 5 ng/mL, and a triplication is 24 ± 6 ng/mL).[40] In addition, 20% of people identified with HAT syndrome have had systemic immediate hypersensitivity reactions to insect stings. Although elevated bST value and insect sting anaphylaxis have been attributed to clonal MC disease, there is a potential role for *TPSAB1* copy number, which requires further investigation.[44,45]

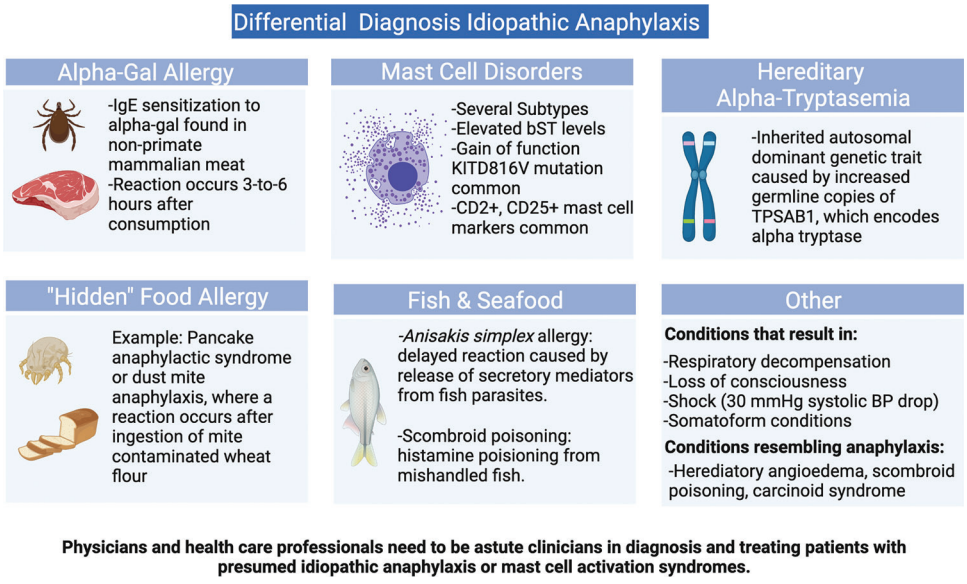

Figure 2. *Differential diagnosis to consider for idiopathic anaphylaxis. Alpha-gal allergy, mast cell disorders (mastocytosis; mast cell activation syndrome: primary, secondary, and idiopathic), hereditary alpha-tryptasemia, "hidden" food allergy (e.g., pancake anaphylactic syndrome, food allergy exercise-induced anaphylaxis), Anisakis simplex allergy, scombroid poisoning, and other conditions that have similar symptoms to anaphylaxis could be considered in cases in which an anaphylactic trigger cannot be identified.*

Others

Pancake anaphylactic syndrome or dust-mite anaphylaxis, in which an anaphylactic reaction occurs after ingestion of mite-contaminated wheat flour, particularly in pancakes, is an example of where "hidden" food allergens can cause anaphylaxis, which may be diagnosed as IA.[46,47] Food-dependent exercise-induced anaphylaxis can be misidentified as IA; in some cases, symptoms occur a few hours after ingesting certain foods in the context of recent exercise.[48] *Anisakis simplex* allergy is a delayed reaction caused by the release of secretory mediators from a fish parasite after it anchors to the gastrointestinal mucosa and is a common cause of anaphylaxis in regions where consumption of rare fish is popular.[49,50] Scombroid poisoning, or histamine fish poisoning, occurs from the consumption of time-temperature abused raw fish, which results from the enzymic conversion of free histidine in fish muscle tissue.

No clear dose-response relationship exists between histamine levels and the reaction, and symptom onset occurs 10 minutes to 1-hour after consumption of poisoned fish, and which usually resolves within 24 hours.[51] Conditions that result in acute respiratory decompensation (*e.g.,* severe asthma, foreign body aspiration, pulmonary embolism), loss of consciousness (*e.g.,* vasovagal reaction, seizure disorder, myocardial infarction, arrhythmias), shock (in which there is at least a 30 mm Hg drop in systolic blood pressure in adults and adolescents), somatoform conditions, or other disorders that resemble anaphylaxis (*e.g.,* hereditary angioedema, scombroid poisoning, carcinoid syndrome) may also be considered as differential diagnoses for IA and may only occur once in a patient's lifetime. Overall, physicians and healthcare professionals need to be astute clinicians in diagnosing and treating patients with presumed IA or MCAS (Fig. 2).

MANAGEMENT OF IDIOPATHIC ANAPHYLAXIS

Acute Management: Epinephrine

Epinephrine is the first-line treatment for anaphylactic reactions of both known and unknown causes, and an epinephrine autoinjector (*e.g.,* EpiPen [Mylan, Canonsburg, Pennsylvania, US], Allerject [Kaleo, Richmond, Virginia, US], AUVI-Q [Kaleo, Richmond, Virginia, US], Emerade [Medeca Pharma AB, Uppsala, Sweden], JEXT [ALK, Horsholm, Denmark]) should be carried by those with IA for acute emergency management.[2,52,53] Rapidly recognizing a reaction and administering epinephrine is life saving; both the α- and β-adrenergic vasoconstrictor effects of the treatment act quickly on many body systems and reverse airway obstruction from mucosal edema, and reverse hypotension and/or shock through chronotropic and ionotropic effects. Furthermore, epinephrine decreases the release of mediators from MCs and basophils. Epinephrine should be injected intramuscularly at a dose of 0.01 mg/kg of a 1:1000 (1 mg/mL) solution to a maximum of 0.3 mg in children and 0.5 mg in adults, although initial doses in Canada and the United States are often 0.15 mg and 0.3 mg, respectively, ideally with the patient in the supine position, unless there is respiratory compromise present, in which case, the patient should remain seated.[2,52–55] Epinephrine can be readministered as needed every 5–15 minutes until symptoms resolve; most patients respond after one or two doses.[2,52,53,55]

Acute Management: Second-Line Therapy for Anaphylaxis

Epinephrine is the first-line therapy for anaphylaxis and continues to be underused. Antihistamines and glucocorticoids are often included as adjunctive therapy to manage cutaneous signs associated with anaphylaxis but should not be administered before or in place of epinephrine.[56] H_1 and H_2 antagonism may provide better and longer-lasting control of skin manifestation than H_1 antagonism alone, and second-generation H_1 antihistamines have less-sedating effects.[56,57] Glucocorticoids, such as methylprednisolone and prednisone, inhibit gene expression and production of new inflammatory mediators through the glucocorticoid receptor complex; however, their slow onset of action and limited data on their combined use with epinephrine and antihistamines have no clear established benefit in the treatment of anaphylaxis, except for reducing hospital admission times.[58–61] Both antihistamines and glucocorticoids have not been shown to prevent biphasic anaphylactic reactions, which can occur 1 to 72 hours after the initial episode.[56,62,63]

Long-Term Management

Long-term management for IA aims to reduce the frequency and severity of the anaphylactic reactions. The evidence to support the use of specific treatments in IA is limited to case and small prospective studies. Clinicians should approach managing their patients with IA on a case-by-case basis under close supervision in a stepwise manner.[14,24]

Histamines and Corticosteroids

Nonsedating second-generation H_1 antihistamines can be used to manage patients with IA and can be adjusted up to four times the licensed dose.[14] H_2 antihistamines and antileukotrienes can be given to patients who are nonresponsive.[14] For adult patients who are IA-frequent, long-term steroid use (40–60 mg of daily prednisone) and H_1-antagonists (10 mg of cetirizine, 25–50 mg of hydroxyzine, 25–50 mg of diphenhydramine, or 180 mg of fexofenadine) have been shown to be useful,[64,65] but, ideally, long-term steroids should be avoided. Commonly cited adverse events associated with long-term corticosteroid use in autoimmune disease, asthma, and lung diseases include hypertension, bone fracture, cataracts, metabolic issues (*e.g.*, weight gain, type 2 diabetes, hyperglycemia), nausea, vomiting, and other gastrointestinal conditions.[66] Daily use of prednisone for 1–2 weeks, followed by decreasing to alternating days may reduce the likelihood of the risks described above.[67]

Some patients who were IA-frequent were stabilized on alternating corticosteroid daily therapy for 3 months to 13 years, whereas others remained corticosteroid dependent.[15] A retrospective study of 35 patients with IA successfully treated 32 patients with antihistamines; only three still had frequent episodes, of which two patients required chronic glucocorticoids use, which demonstrated that antihistamines can be used in patients who were IA-frequent without the need for glucocorticoids.[68] Overall, evaluating the risks versus benefits of corticosteroids in patients who are IA-frequent on a case-by-case basis is salient, second-generation H_1 antihistamines therapy should be prioritized, steroids should be saved as a breakthrough therapy, and these patient should be maintained at the lowest possible dose.[14] Steroids are typically not required for those with the IA-infrequent phenotype.[8,67]

Ketotifen is a second-generation, noncompetitive H_1 antihistamine and MC stabilizer; little evidence has been published on the use of this pharmacotherapy in IA. However, combining ketotifen with an H_1- or H_2-antagonist may be more effective than ketotifen alone.[69–71] The MC-stabilizing properties of ketotifen have also been demonstrated in mastocytosis.[72,73] Ketotifen is superior to doxepin because it does not have sedating effects.[24] Ketotifen, oral cromolyn, or oral albuterol have been trialled in some cases of corticosteroid-dependent IA.[74] There is limited evidence for leukotriene receptor antagonists, *e.g.*, montelukast, to prevent IA, but there is some evidence for its use in urticaria and food-dependent exercise-induced anaphylaxis.[75,76]

Monoclonal Antibodies: Omalizumab, Dupilumab, and Rituximab

The anti-IgE monoclonal antibody (mAb), omalizumab, which blocks the binding of IgE to MCs and basophils, is a well-established treatment for chronic, moderate, and severe persistent asthma, and plays an important therapeutic role in seasonal and perennial allergic rhinitis, chronic rhinosinusitis with and without nasal polyps, and chronic idiopathic urticaria.[77–79] Omalizumab has been successfully used concomitantly with oral immunotherapy to rapidly desensitize people with peanut allergy over an 8-week period, which demonstrated the potential application of this drug in food allergy.[80] A double-blind placebo controlled trial in 19 patients with frequent IA found a modest but not significant trend in reducing anaphylactic events; specifically after 60 days, in the omalizumab group, with a tolerable long-term safety profile.[81] Another study found that four patients with IA experienced a benefit from omalizumab within 4 months.[25] Several case studies found that patients with IA who failed to have their anaphylactic episodes decrease with corticosteroid and antihistamine treatment had fewer or no attacks when provided 300–375 mg of omalizumab once every 2 to 4 weeks, in ~6–12 months.[82–84]

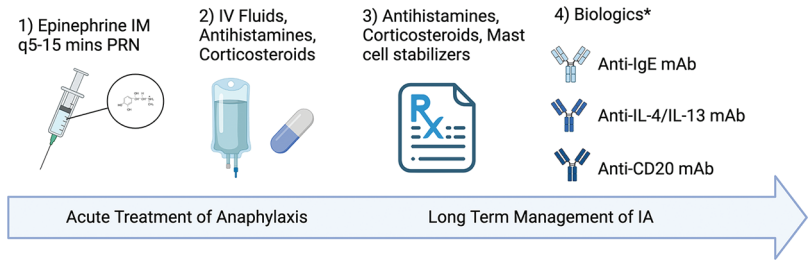

Figure 3. *Acute and long-term management of IA. (1) Epinephrine should be given immediately upon signs of anaphylaxis; epinephrine can be administered intramuscularly every 5 to 15 minutes as needed until the patient is stabilized; intravenous and nebulized epinephrine have also been used in certain circumstances. (2) IV fluids, antihistamines, and corticosteroids are adjunctive therapies in anaphylaxis management but should not be given before or instead of epinephrine. (3) Antihistamines, specifically nonsedating second-generation H_1 antihistamines, corticosteroids, and mast cell stabilizers are some of the medications used to decrease the frequency and severity of IA, although research is limited on their efficacy. (4) Biologics are a potential long-term steroid-sparing treatment for people with IA, so far omalizumab (anti-IgE), dupilumab (anti-IL-4/anti-IL-13), and rituximab (anti-CD20) have been used. *The latter two biologics have only been demonstrated in one case study. IA = Idiopathic anaphylaxis; IV = intravenous; IgE = immunoglobulin-E; IL = interleukin; IM = intramuscular; mAb = monoclonal antibodies; PRN = as needed; q = every.*

Overall, the benefits of omalizumab in IA have been limited to a few cases but may represent a steroid-sparing alternative for patients with IA.[14,25,81,85,86]

Dupilumab, an anti–interleukin (IL) anti IL 4/anti-IL 13 mAb, is approved for T-helper type 2 skewed conditions, such as atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyps.[87] Thus far, one case study on a 23-year-old woman with IA who was successfully treated with 150 mg of dupilumab every 2 weeks after not improving while on 300 mg of omalizumab given every 2 weeks, has been published. IL-4 signaling is a crucial determinant of MC expansion and can trigger anaphylaxis, which provides mechanistic support for the potential use of dupilumab in IA, although more studies are needed.[87] Also, Borzutky *et al.*,[88] proposed the use of rituximab, a chimeric anti-CD20 mAb that targets and depletes circulating B cells, which are elevated in people with IA; however, this treatment has only been demonstrated in one patient (Fig. 3).[88]

CONCLUSION

The lack of diagnostic criteria and the limited treatment options make IA challenging for patients and clinicians to manage. A differential diagnosis such as α-gal allergy, MC disorders, HAT syndrome, hidden food allergens, *Anisakis simplex* allergy, and scombroid poisoning manifests similarly to anaphylaxis and may initially be diagnosed as IA. A knowledgeable healthcare provider must rule out these conditions. Patients with IA must carry an epinephrine autoinjector; second-line treatments for long-term management may include antihistamines and corticosteroids; however, clinical evidence for specific treatments is sparse. Omalizumab, dupilumab, and rituximab are biologics that have shown some potential for use in this patient population.

Summary

- Anaphylaxis is a severe life-threatening allergic reaction that is rapid in onset and requires epinephrine treatment, and has a prevalence of 0.3% to as high as 2%.
- IA is a diagnosis of exclusion based on the inability to identify a causal relationship between a trigger and an anaphylactic event, despite a detailed patient history and careful diagnostic assessment.
- Of people who have experienced anaphylaxis, 10–60% are described as having IA; identifying a cause is crucial.
- Alpha-gal allergy, MC disorders, HAT syndrome, hidden food allergens, *Anisakis simplex* allergy, and scombroid poisoning are differential diagnoses to consider in patients with IA.
- During an anaphylactic episode, the first-line treatment for IA is epinephrine, followed by adjunct antihistamines and corticosteroids to manage cutaneous signs of anaphylaxis.
- Nonsedating second-generation H_1 antihistamines and corticosteroids are used in the long-term management for specific IA cases.
- Omalizumab, dupilumab, and rituximab are biologics that may benefit the patient with IA population; however, more research is urgently needed.

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Figures 1–3 were created with BioRender.com.

REFERENCES

1. Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006; 117:391–397.

2. Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol. 2010; 126:477–480.e1-e42.
3. Kim H, Fischer D. Anaphylaxis. Allergy Asthma Clin Immunol. 2011; 7(suppl 1):S6.
4. Wood RA, Camargo CA Jr, Lieberman P, et al. Anaphylaxis in America: the prevalence and characteristics of anaphylaxis in the United States. J Allergy Clin Immunol. 2014; 133:461–467.
5. Panesar SS, Javad S, Silva D D, et al. The epidemiology of anaphylaxis in Europe: a systematic review. Allergy. 2013; 68:1353–1361.
6. Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis—a practice parameter update 2015. Ann Allergy Asthma Immunol. 2015; 115:341–384.
7. Greenhawt M, Abrams EM, Shaker M, et al. The risk of allergic reaction to SARS-CoV-2 vaccines and recommended evaluation and management: a systematic review, meta-analysis, GRADE assessment, and international consensus approach. J Allergy Clin Immunol Pract. 2021 Jun 18. Epub ahead of print.
8. Nwaru BI, Dhami S, Sheikh A. Idiopathic anaphylaxis. Curr Treat Options Allergy. 2017; 4:312–319.
9. Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy. 2014; 69:1008–1025.
10. Cardona V, Ansotegui IJ, Ebisawa M, et al. World Allergy Organization Anaphylaxis Guidance 2020. World Allergy Organ J. 2020; 13:100472.
11. Yu W, Freeland DMH, Nadeau KC. Food allergy: immune mechanisms, diagnosis and immunotherapy. Nat Rev Immunol. 2016; 16:751–765.
12. Carter MC, Desai A, Komarow HD, et al. A distinct biomolecular profile identifies monoclonal mast cell disorders in patients with idiopathic anaphylaxis. J Allergy Clin Immunol. 2018; 141:180–188.e3.
13. Lenchner K, Grammer LC. A current review of idiopathic anaphylaxis. Curr Opin Allergy Clin Immunol. 2003; 3:305–311.
14. Gulen T, Akin C. Idiopathic anaphylaxis: a perplexing diagnostic challenge for allergists. Curr Allergy Asthma Rep. 2021; 21:11.
15. Ditto AM, Harris KE, Krasnick J, et al. Idiopathic anaphylaxis: a series of 335 cases. Ann Allergy Asthma Immunol. 1996; 77:285–291.
16. Webb LM, Lieberman P. Anaphylaxis: a review of 601 cases. Ann Asthma Immunol. 2006; 97:39–43.
17. Kemp SF, Lockey RF, Wolf BL, et al. Anaphylaxis: a review of 266 cases. Arch Intern Med. 1995; 155:1749–1754.
18. Wright CD, Longjohn M, Lieberman PL, et al. An analysis of anaphylaxis cases at a single pediatric emergency department during a 1-year period. Ann Allergy Asthma Immunol. 2017; 118:461–464.
19. Gonzalez-Estrada A, Silvers SK, Klein A, et al. Epidemiology of anaphylaxis at a tertiary care center: a report of 730 cases. Ann Allergy Asthma Immunol. 2017; 118:80–85.
20. Alonso MAT, Dominguez JS, Sanchez-Hernandez JJ, et al. Idiopathic anaphylaxis: a descriptive study of 81 patients in Spain. Ann Allergy Asthma Immunol. 2002; 88:313–318.
21. Orfan NA, Stoloff RS, Harris KE, et al. Idiopathic anaphylaxis: total experience with 225 patients. Allergy Proc. 1992; 13:35-43.
22. Krasnick J, Patterson R, Meyers GL. A fatality from idiopathic anaphylaxis. Ann Allergy Asthma Immunol. 1996; 76:376–378.
23. Patterson R, Clayton DE, Booth BH, et al. Fatal and near fatal idiopathic anaphylaxis. Allergy Proc. 1995; 16:103–108.
24. Carter MC, Akin C, Castells MC, et al. Idiopathic anaphylaxis yardstick: practical recommendations for clinical practice. Ann Allergy Asthma Immunol. 2020; 124:16–27.
25. Le M, Gabrielli S, De Schryver S, et al. Management strategies of idiopathic anaphylaxis in the emergency room: current perspectives. Open Access Emerg Med. 2019; 11:249–263.
26. Chung CH, Mirakhur B, Chan E, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-α-1,3-galactose. N Engl J Med. 2008; 358:1109–1117.
27. Commins SP, Satinover SM, Hosen J, et al. Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose-α-1,3-galactose. J Allergy Clin Immunol. 2009; 123:426–433.
28. Pattanaik D, Lieberman P, Lieberman J, et al. The changing face of anaphylaxis in adults and adolescents. Ann Allergy Asthma Immunol. 2018; 121:594–597.
29. Young I, Prematunge C, Pussegoda K, et al. Tick exposures and alpha-gal syndrome: a systematic review of the evidence. Ticks Tick Borne Dis. 2021; 12:101674.
30. Gonzalez - Quintela A, Vidal C, et al. IgE antibodies to alpha-gal in the general adult population: relationship with tick bites, atopy, and cat ownership. Clin Exp Allergy. 2014; 44:1061–1068.
31. Jarkvist J, Brockow K, Gülen T. Low frequency of IgE-mediated food hypersensitivity in mastocytosis. J Allergy Clin Immunol Pract. 2020; 8:3093–3101.
32. Akin C, Scott LM, Kocabas CN, et al. Demonstration of an aberrant mast-cell population with clonal markers in a subset of patients with "idiopathic" anaphylaxis. Blood. 2007; 110:2331–2333.
33. Gülen T, Hägglund H, Sander B, et al. The presence of mast cell clonality in patients with unexplained anaphylaxis. Clin Exp Allergy. 2014; 44:1179–1187.
34. Valent P, Akin C, Arock M, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. Int Arch Allergy Immunol. 2012; 157:215–225.
35. Valent P, Akin C, Bonadonna P, et al. Proposed diagnostic algorithm for patients with suspected mast cell activation syndrome. J Allergy Clin Immunol Pract. 2019; 7:1125–1133.e1.
36. Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: proposed diagnostic criteria. J Allergy Clin Immunol. 2010; 126:1099–1104.e4.
37. De Schryver S, Halbrich M, Clarke A, et al. Tryptase levels in children presenting with anaphylaxis: temporal trends and associated factors. J Allergy Clin Immunol. 2016; 137:1138–1142.
38. Álvarez-Twose I, González de Olano D, Sánchez-Muñoz L, et al. Clinical, biological, and molecular characteristics of clonal mast cell disorders presenting with systemic mast cell activation symptoms. J Allergy Clin Immunol. 2010; 125:1269–1278.e2.
39. Sperr WR, Kundi M, Elberink HO, et al. Prognostic factors and survival prediction in 1,088 patients with mastocytosis collected in the Registry of the European Competence Network on Mastocytosis (ECNM Registry). Blood. 2016; 128:396.
40. Lyons JJ. Hereditary alpha tryptasemia: genotyping and associated clinical features. Immunol Allergy Clin North Am. 2018; 38:483–495.
41. Lyons JJ, Sun G, Stone KD, et al. Mendelian inheritance of elevated serum tryptase associated with atopy and connective tissue abnormalities. J Allergy Clin Immunol. 2014; 133:1471–1474.
42. Fellinger C, Hemmer W, Wöhrl S, et al. Clinical characteristics and risk profile of patients with elevated baseline serum tryptase. Allergol Immunopathol (Madr). 2014; 42:544–552.
43. Gonzalez-Quintela A, Vizcaino L, Gude F, et al. Factors influencing serum total tryptase concentrations in a general adult population. Clin Chem Lab Med. 2010; 48:701–706.
44. Bonadonna P, Zanotti R, Müller U. Mastocytosis and insect venom allergy. Curr Opin Allergy Clin Immunol. 2010; 10:347–353.
45. Sturm GJ, Kranzelbinder B, Schuster C, et al. Sensitization to Hymenoptera venoms is common, but systemic sting reactions are rare. J Allergy Clin Immunol. 2014; 133:1635–1643.e1.
46. Sánchez-Borges M, Suárez Chacón R, Capriles-Hulett A, et al. Anaphylaxis from ingestion of mites: pancake anaphylaxis. J Allergy Clin Immunol. 2013; 131:31–35.

47. Sánchez-Borges M, Suárez-Chacon R, Capriles-Hulett A, et al. Pancake syndrome (oral mite anaphylaxis). World Allergy Organ J. 2009; 2:91–96.
48. Asaumi T, Ebisawa M. How to manage food dependent exercise induced anaphylaxis (FDEIA). Curr Opin Allergy Clin Immunol. 2018; 18:243–247.
49. Caballero ML, Asero R, Antonicelli L, et al. Anisakis allergy component-resolved diagnosis: clinical and immunologic differences between patients from Italy and Spain. Int Arch Allergy Immunol. 2013; 162:39–44.
50. Morishima R, Motojima S, Tsuneishi D, et al. Anisakis is a major cause of anaphylaxis in seaside areas: an epidemiological study in Japan. Allergy. 2020; 75:441–444.
51. Hungerford JM. Scombroid poisoning: a review. Toxicon. 2010; 56:231–243.
52. Simons FER, Ardusso LRF, Bilò MB, et al. World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis. World Allergy Organ J. 2011; 4:13–37.
53. Muraro A, Roberts G, Worm M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy. 2014; 69:1026–1045.
54. Sheikh A, Shehata YA, Brown SGA, et al. Adrenaline for the treatment of anaphylaxis: Cochrane systematic review. Allergy. 2009; 64:204–212.
55. Sicherer SH, Simons FER, Section on Allergy and Immunology, American Academy of Pediatrics. Self-injectable epinephrine for first-aid management of anaphylaxis. Pediatrics. 2007; 119:638–646.
56. Shaker MS, Wallace DV, Golden DBK, et al. (2020) Anaphylaxis—a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. J Allergy Clin Immunol. 2020; 145:1082–1123.
57. Hutchcroft BJ, Moore EG, Orange RP. The effects of H1 and H2 receptor antagonism on the response of monkey skin to intradermal histamine, reverse-type anaphylaxis, and passive cutaneous anaphylaxis. J Allergy Clin Immunol. 1979; 63:376–382.
58. Choo KJL, Simons FER, Sheikh A. Glucocorticoids for the treatment of anaphylaxis. Evid-Based Child Health. 2013; 8:1276–1294.
59. Gabrielli S, Clarke A, Morris J, et al. Evaluation of prehospital management in a Canadian emergency department anaphylaxis cohort. J Allergy Clin Immunol Pract. 2019; 7:2232–2238.e3.
60. Liyanage CK, Galappatthy P, Seneviratne SL. Corticosteroids in management of anaphylaxis; a systematic review of evidence. Eur Ann Allergy Clin Immunol. 2017; 49:196–207.
61. Michelson KA, Monuteaux MC, Neuman MI. Glucocorticoids and hospital length of stay for children with anaphylaxis: a retrospective study. J Pediatr. 2015; 167:719–724.e3.
62. Lieberman P. Biphasic anaphylactic reactions. Ann Allergy Asthma Immunol. 2005; 95:217–226; quiz 226, 258.
63. Pourmand A, Robinson C, Syed W, et al. Biphasic anaphylaxis: a review of the literature and implications for emergency management. Am J Emerg Med. 2018; 36:1480–1485.
64. Greenberger PA, Lieberman P. Idiopathic anaphylaxis. J Allergy Clin Immunol Pract. 2014; 2:243–250; quiz 251.
65. Simons FER, Ebisawa M, Sanchez-Borges M, et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. World Allergy Organ J. 2015; 8:32.
66. Rice JB, White AG, Scarpati LM, et al. Long-term systemic corticosteroid exposure: a systematic literature review. Clin Ther. 2017; 39:2216–2229.
67. Guo C, Greenberger PA. Idiopathic anaphylaxis. Allergy Asthma Proc. 2019; 40:457–461.
68. Khan DA, Yocum MW. Clinical course of idiopathic anaphylaxis. Ann Allergy. 1994; 73:370–374.
69. Patterson R, Fitzsimons EJ, Choy AC, et al. Malignant and corticosteroid-dependent idiopathic anaphylaxis: successful responses to ketotifen. Ann Allergy Asthma Immunol. 1997; 79:138–144.
70. Wong S, Patterson R, Harris KE, et al. Efficacy of ketotifen in corticosteroid-dependent idiopathic anaphylaxis. Ann Allergy. 1991; 67:359–364.
71. Kurosawa M, Amano H, Kanbe N, et al. Heterogeneity of mast cells in mastocytosis and inhibitory effect of ketotifen and ranitidine on indolent systemic mastocytosis. J Allergy Clin Immunol. 1997; 100 (pt 2):S25–S32.
72. Póvoa P, Ducla-Soares J, Fernandes A, et al. A case of systemic mastocytosis; therapeutic efficacy of ketotifen. J Int Med. 1991; 229:475–477.
73. Ting S. Ketotifen and systemic mastocytosis. J Allergy Clin Immunol. 1990; 85:818.
74. Bilò MB, Martini M, Tontini C, Mohamed OE, et al. Idiopathic anaphylaxis. Clin Exp Allergy. 2019; 49:942–952.
75. Peroni DG, Piacentini GL, Piazza M, et al. Combined cetirizine-montelukast preventive treatment for food-dependent exercise-induced anaphylaxis. Ann Allergy Asthma Immunol. 2010; 104:272–273.
76. Nettis E, Dambra P, D'Oronzio L, et al. Comparison of montelukast and fexofenadine for chronic idiopathic urticaria. Arch Dermatol. 2001; 137:99–100.
77. Vashisht P, Casale T. Omalizumab for treatment of allergic rhinitis. Expert Opin Biol Ther. 2013; 13:933–945.
78. Tsabouri S, Tseretopoulou X, Priftis K, et al. Omalizumab for the treatment of inadequately controlled allergic rhinitis: a systematic review and meta-analysis of randomized clinical trials. J Allergy Clin Immunol Pract. 2014; 2:332–340.e1.
79. Maurer M, Rosén K, Hsieh H-J, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med. 2013; 368:924–935.
80. MacGinnitie AJ, Rachid R, Gragg H, et al. Omalizumab facilitates rapid oral desensitization for peanut allergy. J Allergy Clin Immunol. 2017; 139:873–881.e8.
81. Carter MC, Maric I, Brittain EH, et al. A randomized double-blind, placebo-controlled study of omalizumab for idiopathic anaphylaxis. J Allergy Clin Immunol. 2021; 147:1004–1010.e2.
82. Pitt TJ, Cisneros N, Kalicinsky C, et al. Successful treatment of idiopathic anaphylaxis in an adolescent. J Allergy Clin Immunol. 2010; 126:415–416; author reply 416.
83. Jones JD, Marney SR, Fahrenholz JM. Idiopathic anaphylaxis successfully treated with omalizumab. Ann Allergy Asthma Immunol. 2008; 101:550–551.
84. Demirtürk M, Gelincik A, Colakoğlu B, et al. Promising option in the prevention of idiopathic anaphylaxis: omalizumab. J Dermatol. 2012; 39:552–554.
85. Sanchez-Valenzuela MC, Garcia-Saucedo JC, Motoa G, et al. Treatment of idiopathic anaphylaxis with omalizumab. Ann Allergy Asthma Immunol. 2019; 123:612–613.
86. Jendoubi F, Gaudenzio N, Gallini A, et al. Omalizumab in the treatment of adult patients with mastocytosis: a systematic review. Clin Exp Allergy. 2020; 50:654–661.
87. Rossavik E, Lam W, Wiens L. M003 Novel use of dupilumab in a patient with idiopathic anaphylaxis. Annals of Allergy, Asthma & Immunology. 2020; 125:S54–5.
88. Borzutzky A, Morales PS, Mezzano V, et al. Induction of remission of idiopathic anaphylaxis with rituximab. J Allergy Clin Immunol. 2014; 134:981–983. □